

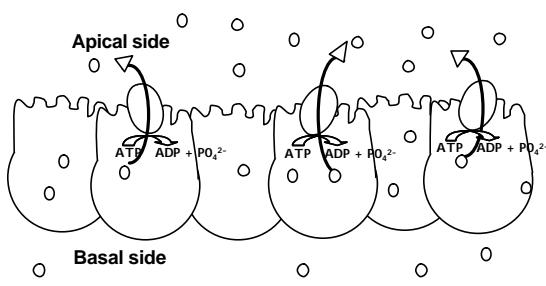
Special Considerations for Individual Biomarkers: P-gp

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Role of Transporters in Drug Response

- Absorption and efflux across the gastrointestinal tract
- Biliary excretion
- Urinary excretion
- Movement across the blood-brain and blood-testes border
- Uptake into target cells
- Target for many commonly prescribed drugs

P-glycoprotein Functions as a Drug Efflux Pump



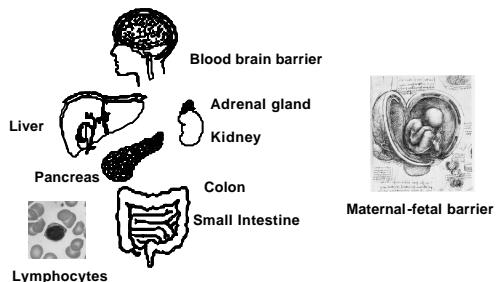
Drugs Which Interact with P-glycoprotein

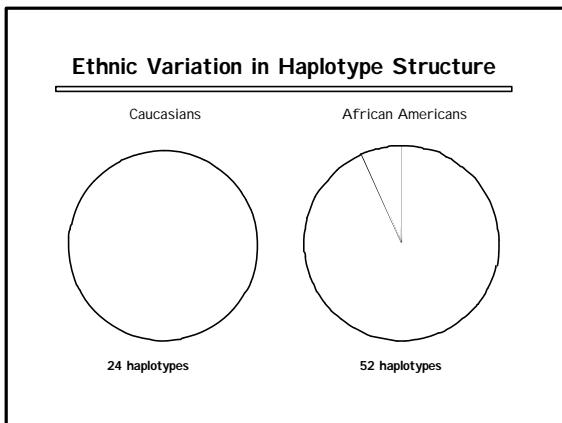
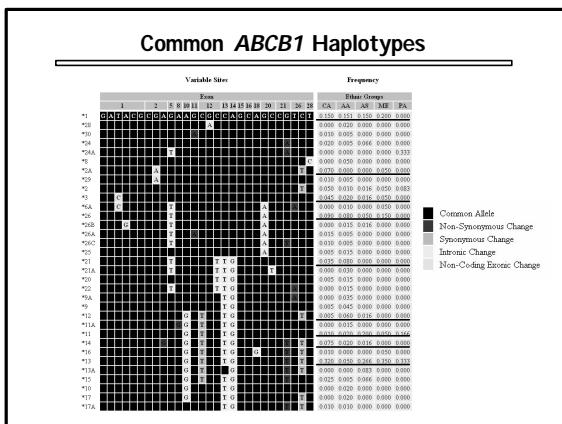
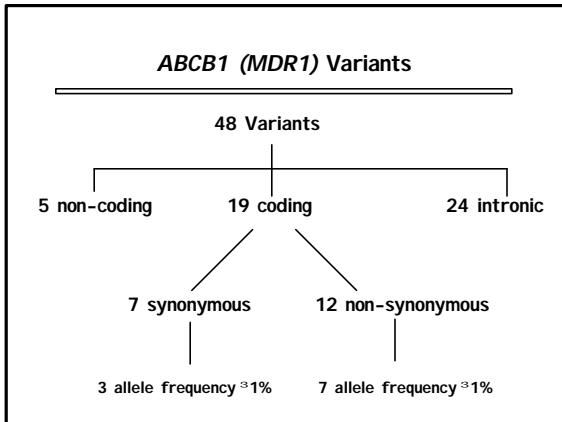
<u>Substrates</u>	<u>Substrates/Inhibitors</u>
Actinomycin D	Mitoxantrone
Colchicine	Paclitaxel
Docetaxel	Teniposide
Doxorubicin	Topotecan
Etoposide	Cortisol
Mitomycin C	Morphine
Digoxin	Loperamide
Fexofenadine	Ivermectin
<u>Inhibitors</u>	<u>Inducers</u>
Ketoconazole	Midazolam
Progesterone	Testosterone
Nifedipine	Dexamethasone
	Rifampin
	St. John's Wort

P-glycoprotein in Cancer

- Intrinsic overexpression - colon, kidney, adrenal, hepatic, and pancreatic cancers and in some leukemias.
- Acquired overexpression subsequent to chemotherapy - breast tumors, ALL, AML, sarcomas and multiple myeloma.
- Increased drug efflux from the tumor cells is one mechanism of resistance to multiple structurally diverse chemotherapeutic agents.

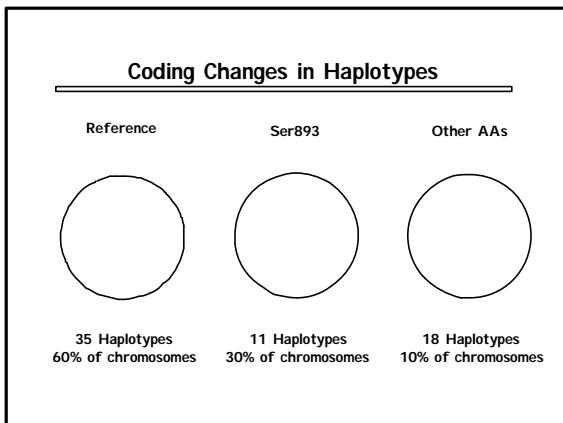
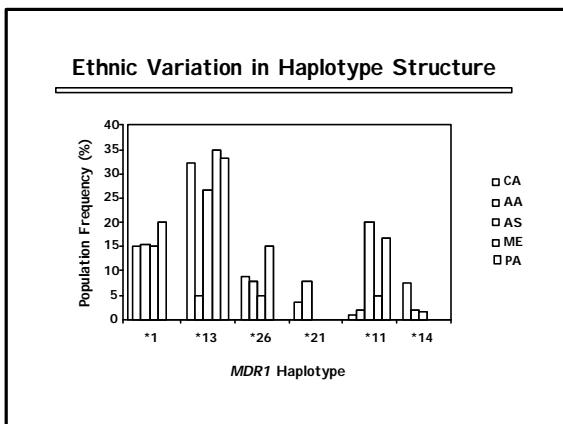
P-glycoprotein Expression in Normal Human Tissues

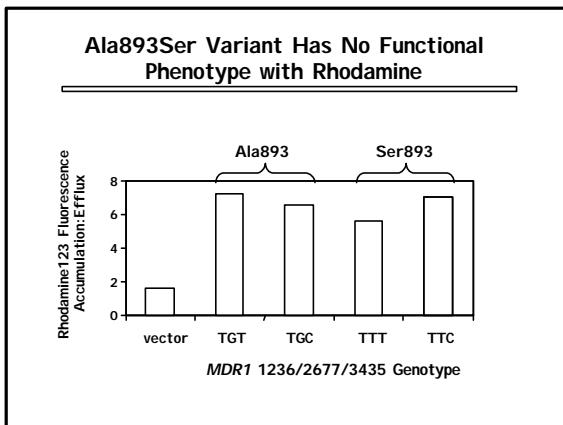
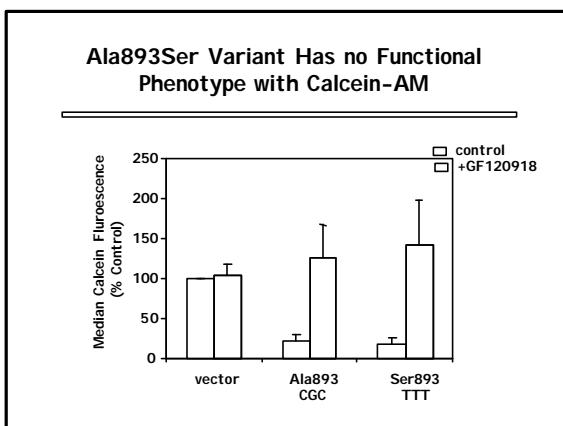
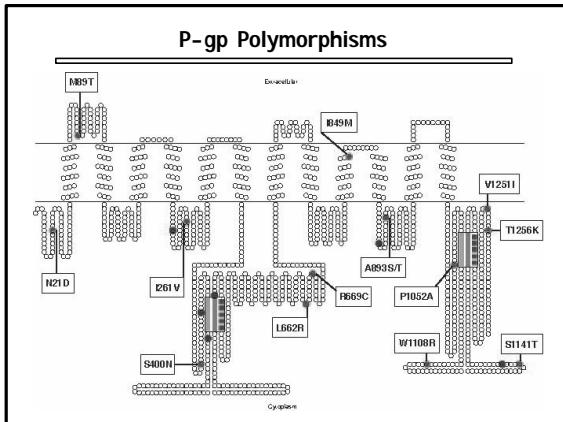


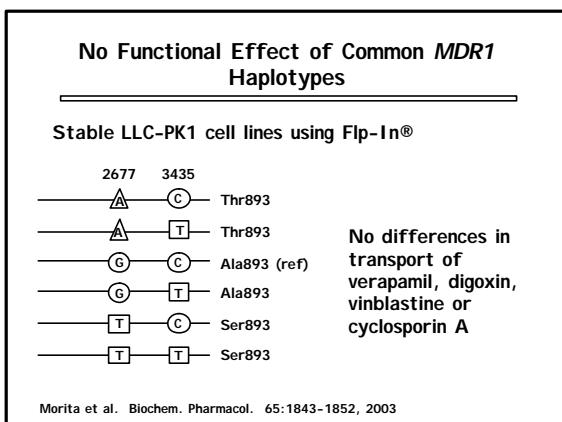
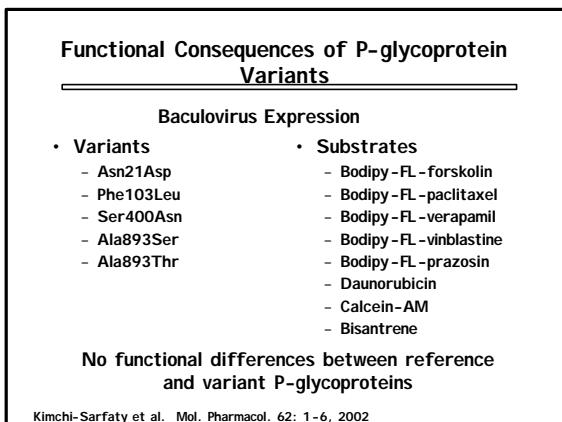
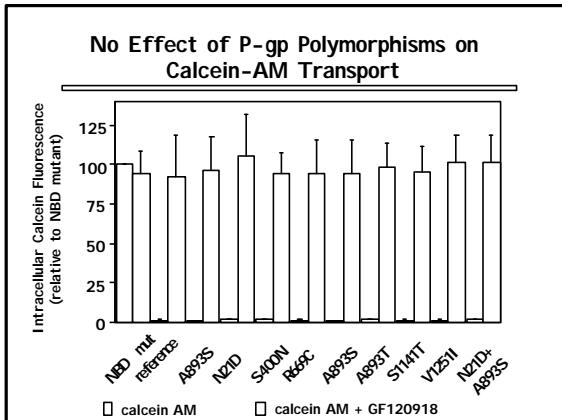


Major *ABCB1* Haplotypes

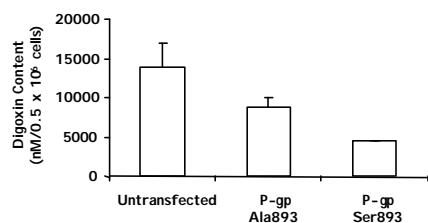
	A61G	G(-25)T Intron 4	A(-44)G Intron 9	C1236T	C(+44)T Intron 12	C(+24)T Intron 13	A(+38)G Intron 14	G(+24)A Intron 20	G2677T	C3435T
*1										
*13										
*26										
*21										
*11										
*14										





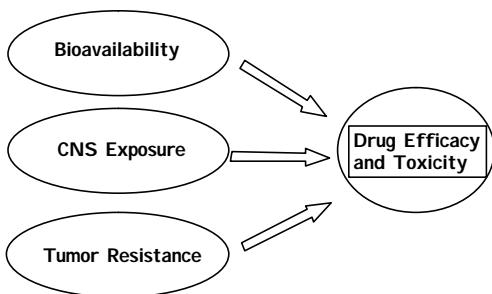


P-glycoprotein Ser893 Variant has Increased Digoxin Transport



Kim et al. Clin Pharmacol Ther 2001; 70:189-199

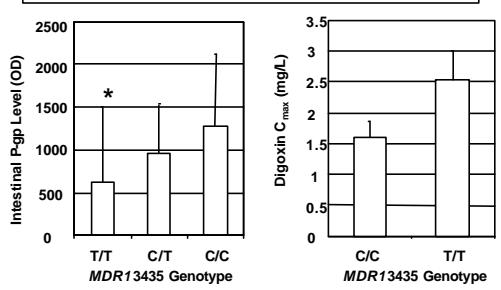
Clinical Significance of P-gp Polymorphisms



Correlation Between *In Vitro* and *In Vivo* Transporter Function???

Correlation Between Genotype and Phenotype???

C3435T Variation is Associated with Decreased Intestinal P-gp and Increased Digoxin Absorption



Hoffmeyer et al. PNAS 97:3473-3478, 2000

C3435T ABCB1 Variant and Digoxin Absorption

- Increased absorption
 - Hoffmeyer et al. 2000
 - Kurata et al. 2002 (2677+3435)
 - Verstuyft et al. (2003)
- Decreased absorption
 - Sakaeda et al. 2001
 - Horinouchi et al. 2002 (2677+3435)
- No effect
 - Bequemont 2001
 - Gerloff et al. 2002
 - Johne et al. 2002 (2677+3435)

Effect of C3435T ABCB1 Variant on Pharmacokinetics

- Fexofenadine
 - ↓AUC (1236+2677+3435) - Kim et al. 2001
 - No change - Drescher et al. 2002
- Antiretrovirals
 - ↓Median drug levels and CD4 cell count - Fellay et al. 2002
 - No effect - Brumme et al. 2003, Winzer et al. 2003
- Cyclosporine
 - No effect - von Ashen et al. 2001, Min et al. 2002
 - No effect of 1236/2677/3435 haplotype - Anglicheau et al. 2004, Haufrord et al. 2004
 - No effect of 2677/3435 haplotype - Mai et al. 2003
 - Conc/Dose ratio with 3435TT - Bonhomme-Favre et al. 2004

Effect of C3435T *ABCB1* Variant on Pharmacokinetics

- Tacrolimus
 - No effect - MacPhee et al. 2002, Goto et al. 2002
 - 2677/3435 haplotype associated with dose requirement - Anglicheau et al. 2003
- Telinolol
 - No effect - Siegmund et al. 2002
- Risperidone
 - No effect of 2677/3435 haplotype - Yasui-Furukori et al. 2004
- Atorvastatin
 - Reduction in LDL and ↑ elevation in HDL - Kajinami et al. 2004

Effect of *ABCB1* Variation on Cancer Phenotype

- 2677T and 3435T genotypes overexpressed in colorectal tumors with high microsatellite instability - Potocnik et al. 2002
- 1236CC/2677GG/3435CC associated with ↓ overall survival and ↑ probability of relapse in adult AML patients - Illmer et al. 2002
- 3435TT genotype overexpressed in renal cell carcinomas - Siegmund et al. 2002
- 3435 genotype not related to drug resistance or prognosis in ALL patients - Efferth et al. 2003

Effect of *ABCB1* Variation on Blood-Brain Barrier Function

- Loperamide - Pauli-Magnus et al. 2003
 - 3435 not associated with respiratory depression
- Nortriptyline - Roberts et al. 2002
 - 3435TT increased risk of postural hypotension
- Tacrolimus - Yamauchi et al. 2002
 - 2677 genotype positive predictor of neurotoxicity
 - 3435 genotype negative predictor of neurotoxicity
- Parkinson's disease - Furuno et al. 2002
 - Increased frequency of 3435TT genotype in early-onset Parkinson's disease patients

What Alleles Should be Genotyped?

- Intronics
 - Intron 4 -G(-25)T
 - Intron 12 - C(+44)T
 - Intron 13 - C(+24)T
 - Intron 14 - A(+38)G
 - Intron 20 - G(+24)A
- UTR
 - T-129C
- Coding
 - A61G (Asn21Asp)
 - C1236T
 - G2677T/A (Ala893Ser/Thr)
 - C3435T
 - T3421A (Ser1141Thr) - African American specific

Are There P-gp Poor Transporters???

SLCO1B1 (OATP1B1)

- OATP1B1 (OATP-C) is an organic anion transporter highly expressed on the basolateral membrane of hepatocytes
- Substrates include bile salts, conjugated and unconjugated bilirubin, steroid conjugates, methotrexate, pravastatin and rifampin

Genetic Polymorphisms in *SLCO1B1*

- At least 6 non-synonymous and two promoter SNPs have been identified
 - T521C (Val174Ala) and G1463C (Gly488Ala) have reduced function *in vitro*
 - A388G (Asn130Asp)/T521A (Val174Ala) haplotype associated with significant reductions in pravastatin CL_{NP}

Tirona et al. 2001, Nozawa et al. 2002, Nishizato et al. 2003, Niemi et al. 2004, Mwinyi et al. 2004

Acknowledgments

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